Malignancy and Active Glomerular Diseases: Debates on Biopsy, Immunosuppression & Dialysis

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Tanta Faculty of Medicine

Agenda:

- Overview.
- Role of biopsy?
- Immunosuppression.
- Dialysis?

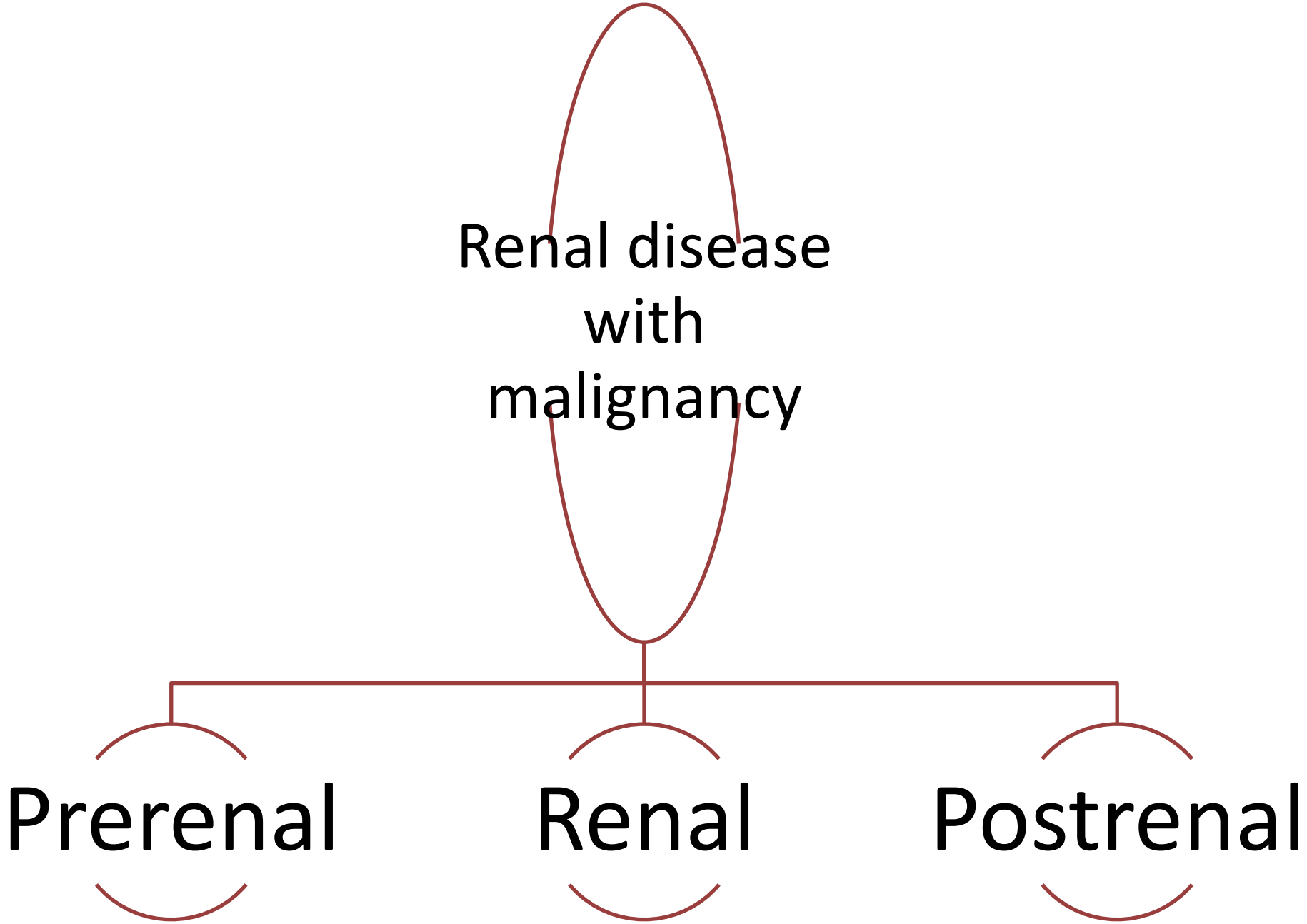
Agenda:

- Overview.

Overview:

- Malignancy or its treatment can produce a variety of renal diseases.
- **Acute and chronic kidney disease and electrolyte abnormalities are the most common.**
- However, nephrotic syndrome, isolated proteinuria, and other syndromes can occur.

Humphreys BD, et al.: J Am Soc Nephrol 2005; 16:151.


Renal disease
with
malignancy
Prerenal
Renal
Postrenal

Overview:

- The association between glomerulonephritis and malignancy was described in clinical series.
- A cancer may be evident before, discovered concomitantly with, or detected well after the development of glomerular lesions.

Burstein, et al. (1993): Am J Kidney Dis 1993 22: 5–10.

Overview:

- The excess cancer rate could be the result of:
  - Underlying undiagnosed tumors whose antigens have initiated glomerulonephritis.
  - Immunosuppressive therapy that initiated tumor cells.
  - Viral infection.

FebBirkeland SA & Storm HH et al. (2003): Kidney Int.;63(2):716-21

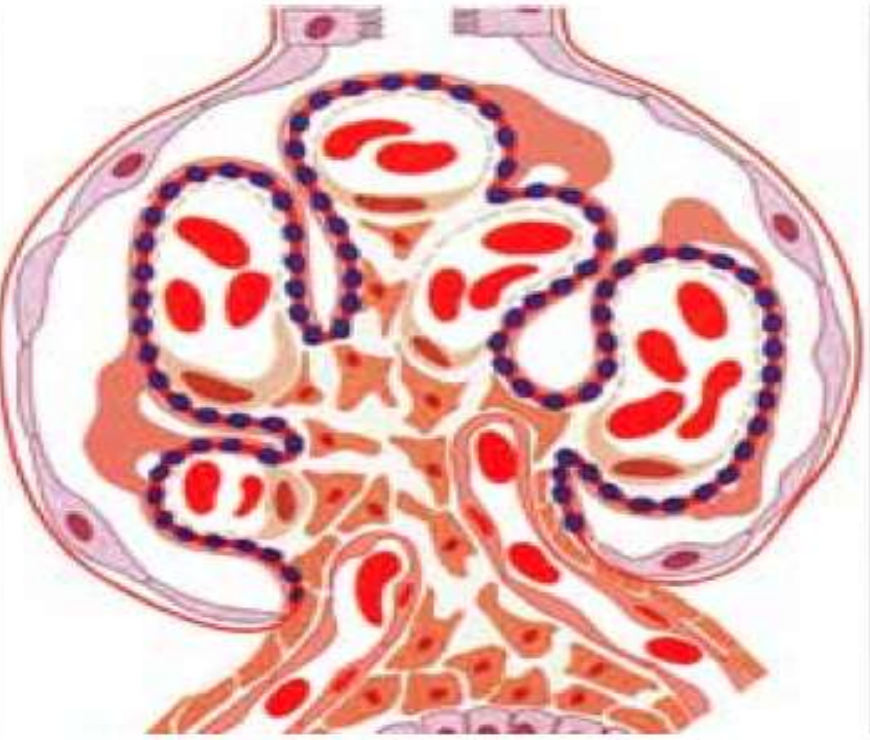
Overview:

- A common virus etiology for both the glomerular disease and the malignancies could be due to:
  - An oncogenic effect of the viruses *per se.*
  - Disturbed clearance of biological mediators of importance for both virus effects and oncogenesis, which are normally cleared in the glomeruli.

FebBirkeland SA & Storm HH et al. (2003): Kidney Int.;63(2):716-21

Overview: Membranous nephropathy

Membranous Nephropathy



- Capillary wall diffusely thickened
- Immune complexes
  - IgG, C3
  - Granular, subepithelial
  - 'Spikes' of basement membrane between deposits

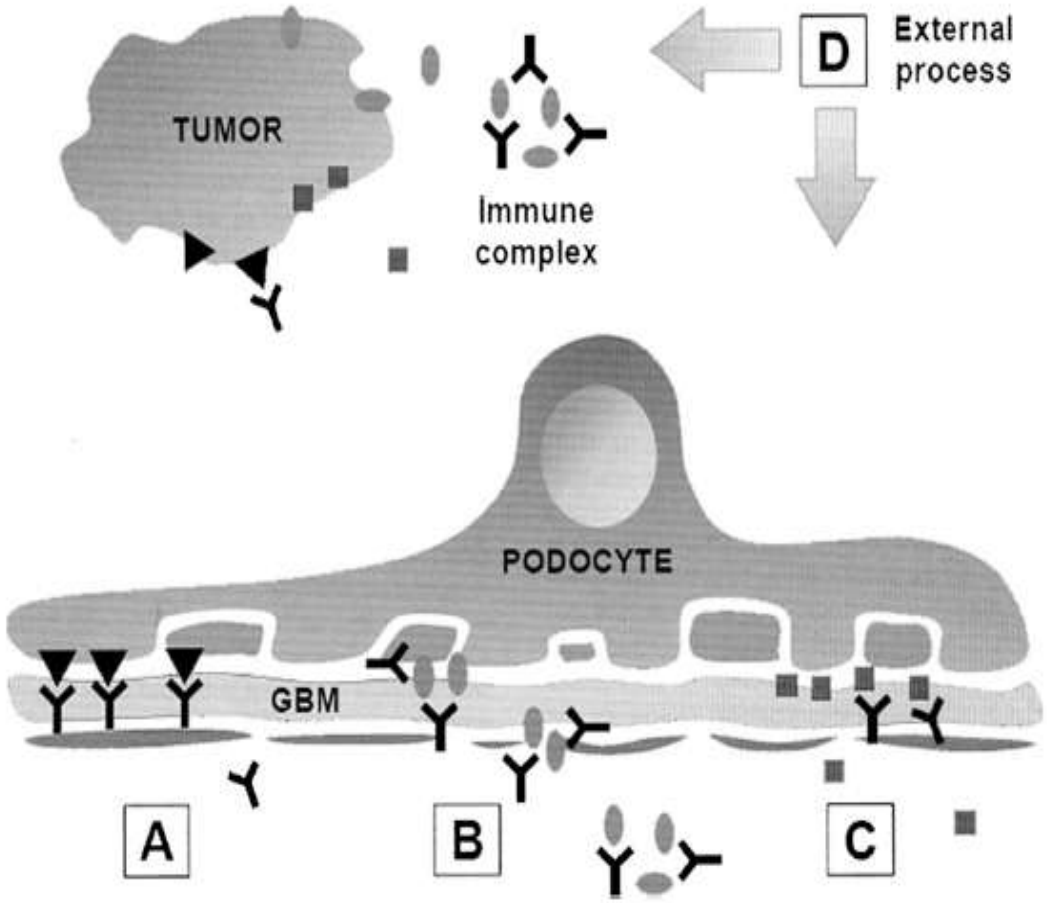


Figure 1. | Mechanisms by which solid tumors and membranous nephropathy (MN) may be linked. MN is defined by subepithelial deposits that form in the glomerular basement membrane (GBM) beneath the foot processes of the glomerular visceral epithelial cell, or podocyte. Antibodies may be generated against an antigen identical to, or bearing an epitope similar to, an endogenous podocyte antigen, thereby leading to *in situ* immune complex formation (A). Alternatively, shed tumor antigens may form circulating immune complexes that become trapped in the capillary wall (B). Complexes may initially form in a subendothelial location, dissociate, and reform in a subepithelial position. Tumor antigens also may, on the basis of size and charge, become planted in a subepithelial location, where they react with circulating antibodies at a later stage (C). Finally, extrinsic processes, such as infection with an oncogenic virus or altered immune function (D), potentially could cause both malignancy and MN. From reference 14, with permission.

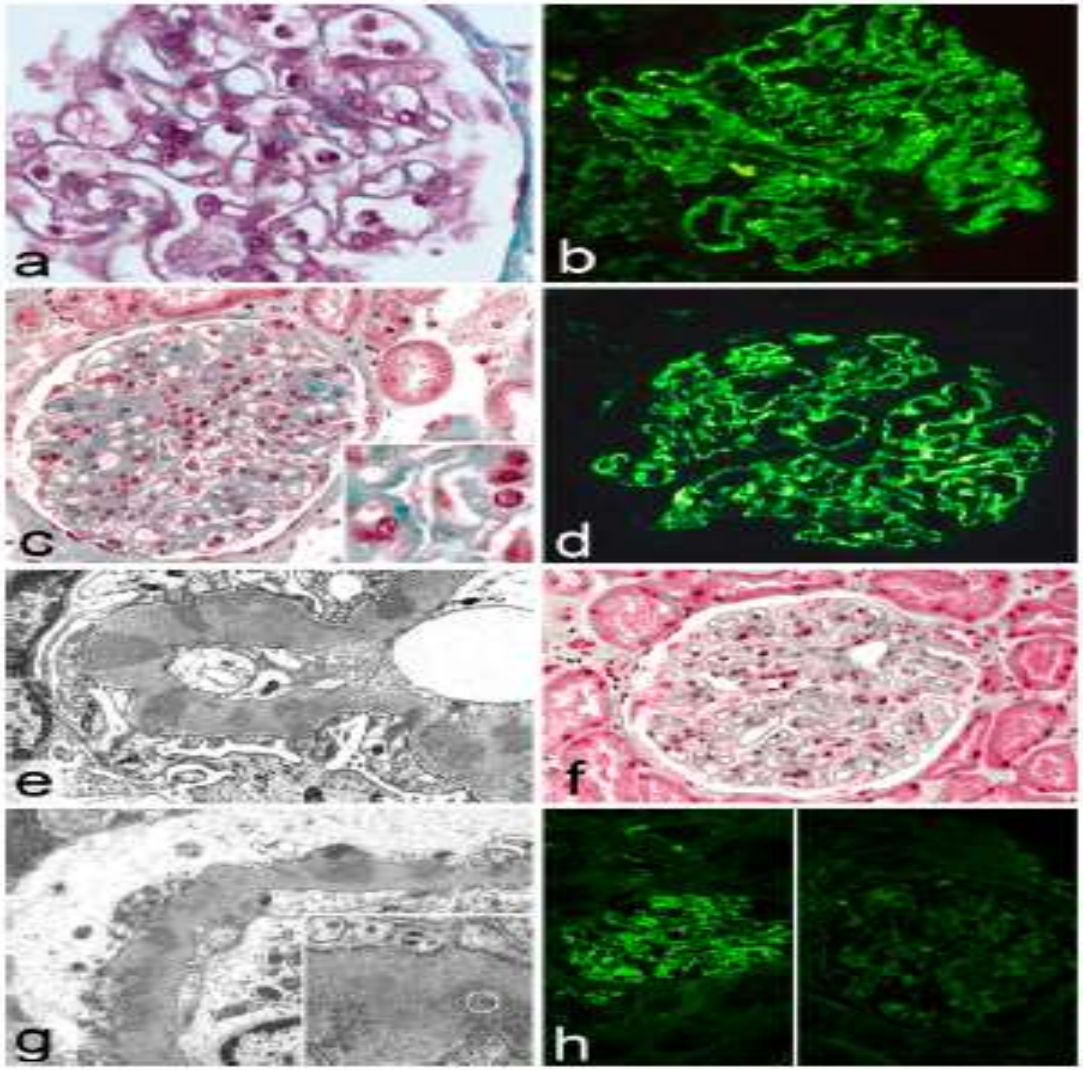


Figure 2. | Glomerular diseases occurring during several malignancies and showing membranous nephropathy histologic patterns. Light microscopy findings in a patient who developed membranous nephropathy in the setting of bronchogenic carcinoma, showing inflammatory cells infiltrating the glomeruli (A) (Masson trichrome stain) and, by immunofluorescence, typical subepithelial deposits (B) (immunofluorescence with anti-γ antibody). A second patient followed for chronic lymphocytic leukemia (CLL) developed proliferative GN with nonorganized monoclonal immunoglobulin deposits defined by immune deposits on the external aspect of the glomerular basement membrane with frequent mesangial hypertrophy on light microscopy (C) (Masson trichrome stain); the deposits have irregular size (inset of C), have a parietal granular distribution by immunofluorescence (D) (immunofluorescence with anti-γ antibody), and are nonorganized in the subepithelial space on ultrastructural study (E). The kidney biopsy specimen of another patient with CLL shows atypical membranous nephropathy: note segmental mesangial and cellular proliferation (F) (Masson trichrome stain). Diffuse granular deposits were found along the capillary walls with predominant subepithelial location, staining exclusively for IgG and κ light chain by immunofluorescence (H) (immunofluorescence with anti-κ antibody on the left panel; in the right, note the absence of deposits with anti-λ antibody) and showing microtubular substructure on ultrastructural studies, as described previously in immunotactoid glomerulopathy (G). Parts C–E from reference 53, with permission. Original magnifications: A, ×1000; B, C, D, and F, ×400; E and G, ×20,000; G inset, ×50,000; H, ×200.

Overview: Membranous nephropathy

- Membranous nephropathy, characterized by proteinuria or the nephrotic syndrome.
- It may be associated with solid tumors, such as carcinoma of the breast, lung or colon, and, less frequently, with a hematologic malignancy such as chronic lymphocytic leukemia.

Timmermans SA, et al.(2013): Am J Kidney Dis 2013; 62:1223.
Burstein DM, et al. (1993): Am J Kidney Dis; 22:5.

Overview: Membranous nephropathy

- The **anti-PLA2R** antibody test is negative or the kidney histology is consistent with secondary MN, and if there is no other clear cause of secondary MN, then such patients may require, more frequent age-appropriate screening for malignancy.

Timmermans SA, et al.(2013): Am J Kidney Dis 2013; 62:1223.
Burstein DM, et al. (1993): Am J Kidney Dis; 22:5.

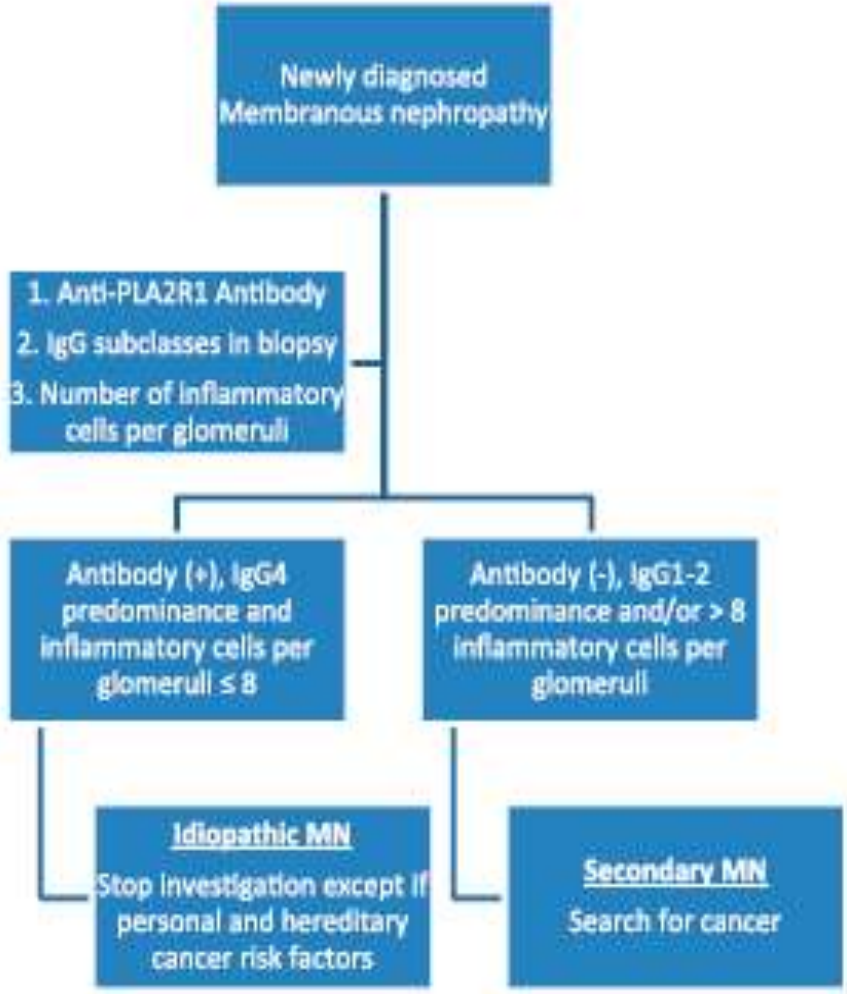
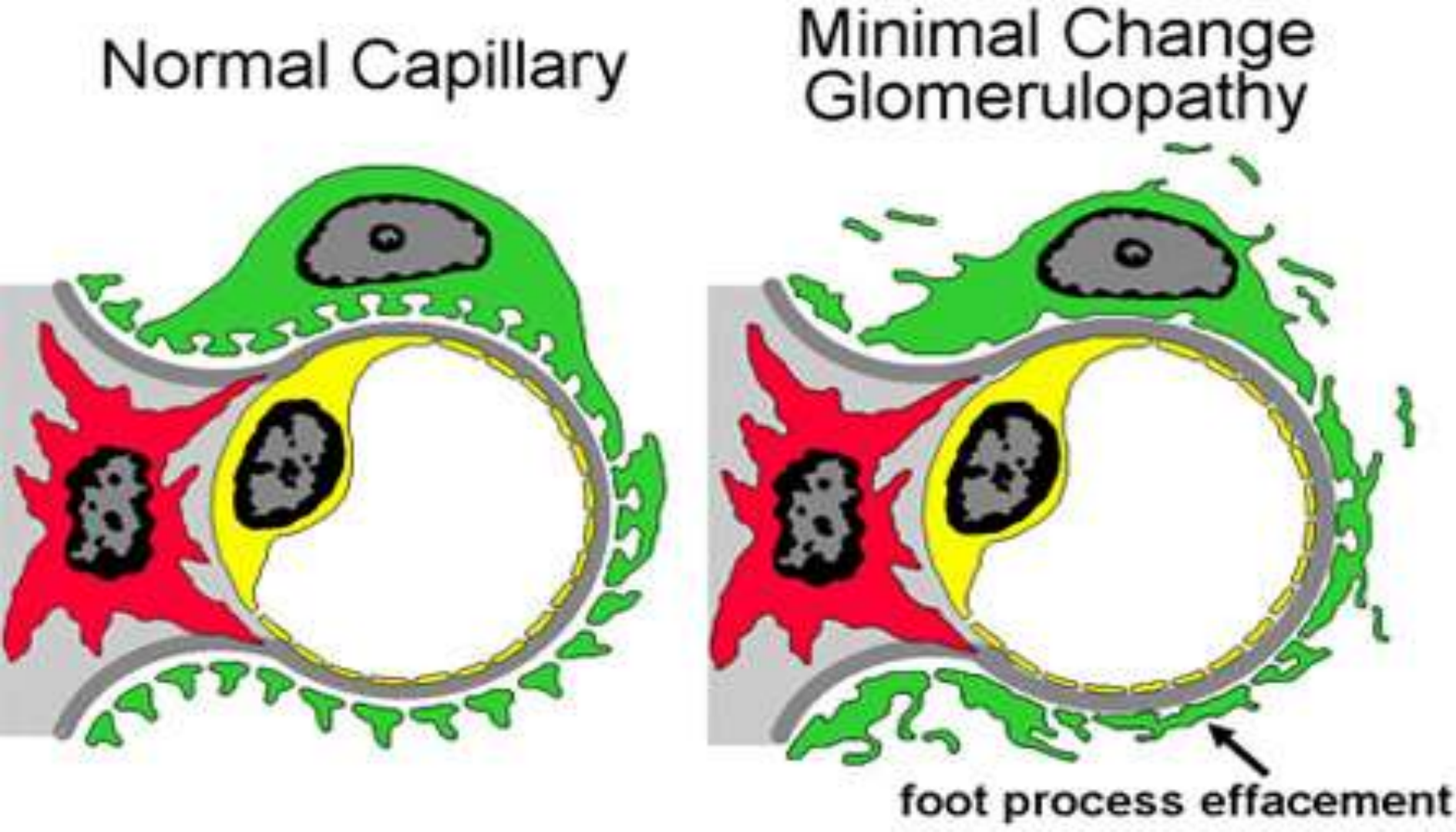


Figure 3. | Management of newly diagnosed membranous nephropathy. In patients with anti-PLA2R1 antibody AND predominant IgG4 deposits AND with few or no inflammatory cells in the glomerulus, a diagnosis of cancer related to MN is unlikely. Further investigations could be stopped except in the presence of cancer risk factors. In patients without anti-PLA2R1 antibody, in those with prevailing IgG1/IgG2 deposits, or in the presence of more than 8 inflammatory cells per glomeruli, a search for cancer should be performed. PLA2R1, phospholipase A2 receptor 1; MN, membranous nephropathy.

Overview: Minimal change disease



Overview: Minimal change disease

- Minimal change disease may occur in association with Hodgkin lymphoma and, less commonly, other lymphoproliferative disorders.
- The mechanism is secretion of a glomerular-toxic lymphokine by abnormal T cells.

Audard V, et al. (2006): Kidney Int 2006; 69:2251.

Overview: Minimal change disease

- The degree of proteinuria usually parallels that of the malignancy, with the proteinuria disappearing when remission of the malignancy is obtained with radiotherapy and chemotherapy

Audard V, et al. (2006): Kidney Int 2006; 69:2251.

Overview: **Proliferative/crescentic GN**

- Both have been described in isolated patients with solid tumors and lymphomas, although the etiologic relationship between these conditions is not proven

Alpers CE, et al. (1986): Kidney Int; 30:465.
Birkeland SA, et al. (2003): Kidney Int; 63:716.

Overview: Proliferative/crescentic GN

- There is some evidence that malignancy is more frequent in patients diagnosed with ANCA vasculitis compared with the general population or with those who have other forms of vasculitis

Alpers CE, et al. (1986): Kidney Int; 30:465.
Birkeland SA, et al. (2003): Kidney Int; 63:716.

Overview: **Proliferative/crescentic GN**

- Mechanism:
  - Dysregulated T-cell response.
  - Elaboration of various cytokines.
  - Uteroglobin, a small molecule , that is expressed by most epithelia such as lung, prostate and endometrium,
  - Uteroglobin is markedly reduced in several carcinomas and was found to be chiefly responsible for invasive growth of epithelial tumours cells

Sibylle von Vietinghoff, et al. (2006): Nephrol Dial Transplant; 21: 3324–3326

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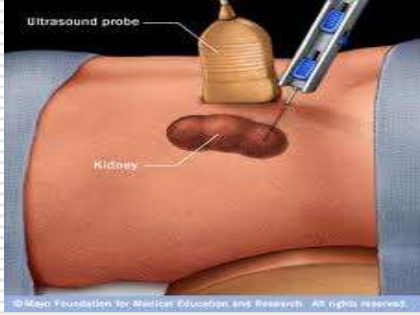
Agenda:

- Role of biopsy?

Role of renal biopsy:



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1. **Renal Pathology**: SY23-1 CURRENT APPROACH TO CLASSIFICATION OF MEMBRANOPROLIFERATIVE **GLOMERULONEPHRITIS**.
Nast CC.
Pathology. 2014 Oct;46 Suppl 2:S41. doi: 10.1097/01.PAT.0000454227.67748.7b.
PMID: 25188169 [PubMed - in process]
Related citations

2. Membranous nephropathy with crescents in a patient with Hashimoto's thyroiditis: a case report.
Thajudeen B, John SG, Ossai NO, Riaz IB, Bracamonte E, Sussman AN.
Medicine (Baltimore). 2014 Aug;93(8):e63. doi: 10.1097/MD.0000000000000063.
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3. Lupus-like membranous nephropathy: Is it lupus or not?
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Clin Exp Nephrol. 2014 Jul 4. [Epub ahead of print]
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4. [A case of nephrotic syndrome during TS-1 therapy after resection of rectal cancer and liver

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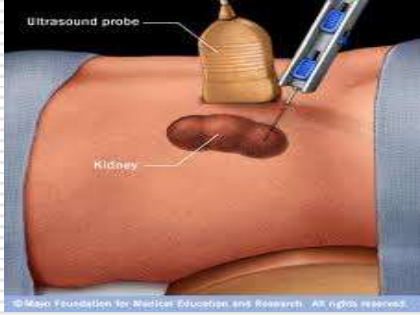

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1 Renal Pathology: SY23.1 CURRENT APPROACH TO CLASSIFICATION OF MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Nasr SH.

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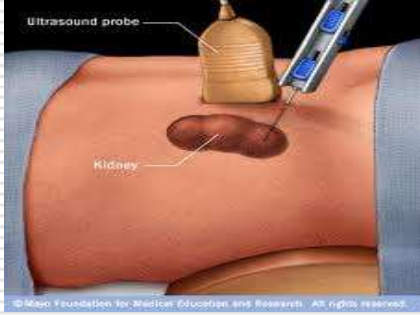

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- Immunosuppression.

Immunosuppression

Role of Immunosuppression:

- When induced by tumor antigens, effective treatment of the malignancy generally leads to improvement in the glomerular injury.
- Conversely, treatment of glomerular disease with drugs such as **cycolphosphamide** can induce cancer, although this typically arises years later.

FebBirkeland SA & Storm HH et al. (2003): Kidney Int.;63(2):716-21

Role of Immunosuppression

- **Mechanisms of alkylating agent-induced malignancy** include direct chromosomal damage and decreased immune surveillance.
- **The duration of therapy** is an important risk factor, with the incidence being greatest in patients treated for more than two to three years

Radis CD, et al. (1995): Arthritis Rheum; 38:1120.

Role of immunosuppression:

- **Collapsing focal segmental glomerulosclerosis (FSGS)** has been associated with exposure to high doses of intravenous bisphosphonates, particularly **pamidronate**, in patients with cancer.

Perazella MA, et al. (2008): Kidney Int; 74:1385.
Markowitz GS, et al. (2001): J Am Soc Nephrol; 12:1164.

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- Dialysis?

Dialysis:

- Patients with GN and malignancy generally follow guideline for dialysis recommended for the general population.
- However, special concern exist for dialysis in cancer patients, due to higher mortality and worse prognosis.

Dialysis:

- AKI complicating cancer is associated with substantial morbidity and mortality.
- Among critically ill cancer patients, 12-49% experience AKI, 9-32% require RRT during their stay in the ICU.
- Hospital mortality rates are high in cancer patients with AKI esp. when RRT is required.
- Given the high mortality rate, physicians might be reluctant to offer RRT to patients with cancer.

Intensive Care Medicine
May 2007, Volume 33, Issue 5, pp 765–772

Date: 07 Mar 2007

Should dialysis be offered to cancer patients with acute kidney injury?

Michael Darmon, Guillaume Thiery, Magali Ciroldi, Raphaël Porcher, Benoît Schlemmer, Élie Azoulay

- The etiology of AKI was multiple in most patients. Hospital mortality was 51.1%.
- Two variables were independently associated with hospital mortality: the severity of associated organ failures at ICU admission and renal function deterioration after ICU admission.

Darmon M, et al. (2007): Intensive Care Med.;33(5):765-72.

Controversy always exists!!!:

Thank You
Thank You
Thank You!!!!